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# Holoprosencephaly in the west of Scotland 1975–1994

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**Abstract**

**Cases of holoprosencephaly which occurred in the west of Scotland over the past 20 years were ascertained from genetics, paediatric, and pathology department records. Fifty cases were identified of which 17 had an underlying cytogenetic abnormality. Of the remaining 33 cases, 26 were delivered after 28 weeks' gestation giving a birth prevalence of 1 in 26 730. Twenty-one babies were liveborn and nine children are currently alive. All survivors are profoundly mentally retarded and most have seizures. Twenty-eight patients with non-chromosomal holoprosencephaly had a total of 23 sibs and three families were identified where there was either recurrence of holoprosencephaly (one family), a related cerebral malformation (one family), or mental handicap (one family) giving an overall recurrence risk for serious neurological disability of 12% (standard error 7%). We conclude that holoprosencephaly does not necessarily breed true and this observation should be taken into account when giving genetic counselling and attempting ultrasound prenatal diagnosis after the birth of an affected child**

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Key words: holoprosencephaly; frequency; recurrence risk.

Holoprosencephaly is a congenital malformation which encompasses a spectrum of abnormalities affecting the forebrain and midface. Its mildest form comprises orbital hypotelorism, a single central incisor, and arrhinencephaly (absence of the olfactory bulbs and tracts), whereas its most severe manifestation is the cyclops phenotype with complete failure of division of the embryonic forebrain into right and left cerebral hemispheres.[1] Estimates of the birth incidence of holoprosencephaly lie between 1:1600[2] and 1:53 394[3] and a study from south-west England found incidences of 1:14 520 and 1:5200 in two consecutive three year periods.[4] Most cases of holoprosencephaly occur sporadically and published reviews have suggested that approximately 50% of cases are associated with chromosome abnormalities, trisomy 13 being the commonest chromosomal cause.[5] Nevertheless, sparse data are available on the frequency of holoprosencephaly associated with cytogenetic abnormalities compared with the frequency of non-chromosomal holoprosencephaly and a detailed population based, clinical genetic study of this cerebral malformation has not previously been reported.[6]

Genetic counselling advice given to couples who have had one child affected by holoprosencephaly is complicated by the malformation's heterogeneity. Both autosomal recessive and autosomal dominant gene defects are reported but X linked holoprosencephaly is especially rare.[7–10] Dominantly inherited holoprosencephaly has variable expression and can be difficult to diagnose since only subtle signs, such as reduced head circumference or a single central incisor, may indicate the mildly affected parent of a severely affected child. Teratogenic factors or maternal illness, especially maternal insulin dependent diabetes mellitus, may also predispose to holoprosencephaly.[11] Usually, genetic advice is empirical and often refers to an American study of 30 families with liveborn, cytogenetically normal children affected by holoprosencephaly, who were assessed at the Indiana University Medical Center between 1957 and 1970. In this study, Roach *et al*[2] derived a recurrence risk for holoprosencephaly of 6%, the figure which is quoted today by many clinical geneticists.

The present study aimed to identify all cases of holoprosencephaly which have occurred in the west of Scotland over a 20 year period, to assess the circumstances of the malformation's diagnosis, its frequency, and its clinical associations. We also sought to discover whether close relatives of an affected person were affected by cerebral malformation or neurological disability to help clarify genetic counselling implications following the birth of an affected fetus or infant.

## Setting and methods

The west of Scotland has an estimated population of just under 3 million. The area included in this study is that served by five regional health boards: Argyll and Clyde, Ayrshire and Arran, Forth Valley, Greater Glasgow, and Lanarkshire. Over 90% of paediatric deaths are referred to the Royal Hospital for Sick Children in Glasgow for necropsy; a small number of paediatric necropsies are also carried out in two of the other health board areas. The Glasgow pathology department currently obtains consent for necropsy for approximately 80% of all childhood deaths and fetal losses.

Patients (fetuses, infants, and children) were ascertained through examination of day books and records from local pathology departments and paediatric departments as well as the files of the regional paediatric neurology and genetic

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*Table 1 Number of cases of holoprosencephaly 1975–1994 and karyotype abnormalities*

| *Karyotype* | *No of patients* |
|---|---|
| Normal | 26 |
| Trisomy 13 | 13 |
| 13q12-q14 deletion | 1 |
| 13q22 or 31 deletion* | 1 |
| 7q34 or 35-qter deletion* | 1 |
| 7q36-qter deletion | 1 |
| Failed culture | 4 |
| Not available | 3 |

* Precise breakpoints could not be determined.

*Table 2 Frequency of non-chromosomal holoprosencephaly throughout the west of Scotland. Note the apparent low frequency in Forth Valley may be real or simply reflect misdiagnosis of one or two cases in a less populous area where no cases of holoprosencephaly were recorded in local pathology department files and the solitary case identified was a liveborn child diagnosed at the regional referral hospital*

| *Health board* | *No of births** | *Cases of HPE* | *Frequency of HPE* |
|---|---|---|---|
| Argyll and Clyde | 117 891 | 8 | 1:14 736 |
| Ayrshire and Arran | 97 090 | 5 | 1:19 415 |
| Forth Valley | 68 545 | 1 | 1:68 545 |
| Greater Glasgow | 256 554 | 12 | 1:21 380 |
| Lanarkshire | 154 870 | 7 | 1:22 124 |
| Total west of Scotland | 694 950 | 33 | 1:21 059 |

* Total births (livebirths and stillbirths) supplied by Vital Statistics Branch, General Register Office for Scotland, Edinburgh.

departments. The patients selected for this study were those diagnosed as having holoprosencephaly/arrhinecephaly on CT scan or at necropsy or both and who were born between years 1975 and 1994. The obstetric case notes of the mothers were studied to obtain details of the pregnancy and delivery, and probands' paediatric case notes were reviewed. General practitioners of the mothers were contacted by letter in order to obtain information about the health of other members of the family and to confirm the number of sibs of each index case. Eleven surviving patients (two of whom subsequently died) were personally examined by the authors.

## Results

### CASES AND CYTOGENETIC ANALYSIS

Throughout the 20 year period, 50 cases of holoprosencephaly occurred giving an overall frequency of 1:14 000. Eighteen patients were ascertained from the genetic department database, 16 from pathology department records, and 12 from the paediatric neurology department database. One patient's name was found from all three sources and 15 patients' names were found in two of the three sources. Cytogenetic results were available for 43 patients (table 1).

The first of two cases with 13q deletions was detected after amniocentesis was performed because of increased Down syndrome risk (1 in 34) from maternal serum screening; the pregnancy was subsequently terminated. The other patient was a liveborn child who survived for 14 days. Two patients had 7q deletions which included band 7q36, the location of the designated HPE3 gene.[12] These cases were also diagnosed by amniocentesis following abnormal maternal serum screening results and the observation of abnormalities on ultrasound scanning. Both pregnancies were subsequently terminated at 22 weeks' gestation. One fetus had a cyclops phenotype while the other had lobar holoprosencephaly.

Patients known to have chromosomal abnormalities were excluded from further analysis of the results and the following refers to the remaining 33 patients, 26 of whom had proven normal karyotypes and seven in whom cultures failed or cytogenetic analysis was not attempted.

### FREQUENCY

Table 2 shows the frequency of non-chromosomal holoprosencephaly for each health

*Table 3 Pregnancy outcome*

| *Case* | *Year* | *Pregnancy outcome* | *Gestation (wk)* | *Birth weight (g)* | *Weight centile* | *Maternal age (y)* | *Paternal age (y)* | *Prenatal diagnosis* |
|---|---|---|---|---|---|---|---|---|
| 1 | 1975 | Livebirth | 40 | 3680 | 50th | 26 | 26 | No |
| 2 | 1977 | Livebirth | 35 | 1020 | 25–50th | 33 | 27 | No |
| 3 | 1978 | TOP | 36 | 1130 | <3rd | N/A | N/A | Yes (36 wk) |
| 4 | 1979 | TOP | 18 | 80 | N/A | N/A | N/A | Yes (18 wk) |
| 5 | 1980 | Stillbirth | 32 | 1200 | 3rd | 20 | N/A | No |
| 6 | 1981 | TOP | 20 | 175 | N/A | 31 | N/A | Yes (20 wk) |
| 7 | 1982 | Livebirth | 31 | 1030 | 3rd | 23 | 35 | No |
| 8 | 1984 | TOP | 17 | 77 | N/A | 28 | N/A | Yes (17 wk) |
| 9 | 1985 | Livebirth | 39 | 3374 | 75th | 26 | 27 | No |
| 10 | 1986 | Livebirth | 41 | 3100 | 25th | 25 | 27 | No |
| 11 | 1986 | Livebirth | 34 | 2200 | 50th | 24 | 26 | No |
| 12 | 1987 | Livebirth | 35 | 2070 | 10–25th | 19 | N/A | No |
| 13 | 1987 | Missed abortion | 16 | 144 | N/A | 24 | N/A | No |
| 14 | 1987 | Stillbirth | 31 | 800 | <3rd | 27 | 29 | No |
| 15 | 1987 | Livebirth | 38 | 2800 | 25–50th | 24 | N/A | No |
| 16 | 1987 | Livebirth | 40 | 3040 | 25–50th | 38 | N/A | No |
| 17 | 1988 | Livebirth | 40 | 2920 | 25th | 22 | 25 | No |
| 18 | 1988 | Livebirth | 31 | 1700 | 97th | 26 | N/A | No |
| 19 | 1989 | Livebirth | 41 | 3120 | 25th | 27 | N/A | No |
| 20 | 1990 | Livebirth | 38 | 2080 (Twin) | <3rd | 23 | 27 | Yes (28 wk) (Dizygotic) |
| 21 | 1991 | Livebirth | 40 | 2760 | 3rd | 34 | N/A | No |
| 22 | 1991 | Stillbirth | 33 | 1320 | <3rd | 34 | 36 | No |
| 23 | 1991 | Livebirth | 40 | 3660 | 50–75th | 20 | N/A | No |
| 24 | 1991 | Livebirth | 34 | 2620 | 75–90th | 36 | 36 | No |
| 25 | 1991 | Livebirth | 35 | 1960 | 25th | 25 | 25 | No |
| 26* | 1992 | TOP | 19 | 328 | N/A | 26 | 25 | Yes (19 wk) |
| 27 | 1993 | Livebirth | 36 | 3400 | 97th | 27 | 28 | Yes (30 wk) |
| 28 | 1993 | Livebirth | 38 | 2640 | 25–50th | 20 | 20 | No |
| 29 | 1993 | Livebirth | 40 | 4320 | >97th | 22 | 23 | No |
| 30 | 1993 | TOP | 22 | 335 | N/A | 39 | N/A | Yes (22 wk) |
| 31* | 1993 | Livebirth | 38 | 2560 | 25–50th | 27 | 26 | No |
| 32 | 1994 | TOP | 34 | 1490 | 50th | 24 | 26 | Yes (32 wk) |
| 33 | 1994 | TOP | 25 | 660 | 10th | 27 | 26 | Yes (25 wk) |

* Sib-pair. N/A = information not available.

board area and for the whole region. Twenty-six infants were delivered after 28 weeks' gestation giving a birth prevalence of 1 in 26 730.

PREGNANCY OUTCOME

Obstetric case notes for 30 of the 32 mothers were examined. One mother was identified as having two children with holoprosencephaly and in two cases there was insufficient information available from necropsy reports for the obstetric case notes to be traced. Information regarding the parents, pregnancies, and birth details is summarised in table 3.

CLINICAL FEATURES

The clinical features of the affected children and fetuses are summarised in table 4. This

*Table 4 Clinical features, classification, survival, and sibs*

| Case | Karyotype | Sex | Clinical features | Severity of HPE | Age at death | Age now (y) | Position in family | Later sibs |
|---|---|---|---|---|---|---|---|---|
| 1 | 46, XY | M | Microcephaly, epicanthic folds, oblique palpebral fissures, malformed ears, micrognathia, midface hypoplasia, high arched palate, talipes, pectus excavatum, hypoplastic genitalia, seizures | Semilobar | 3 y | | 2nd | 0 |
| 2 | 46, XY | M | Microcephaly, arrhinencephaly, cerebellar hypoplasia, absent nose, bilateral cleft lip and palate, bilateral simian creases, absent digit 1 foot | Alobar | 13 h | | 2nd | 1 |
| 3 | 46, XY | M | Encephalocele, absent pituitary gland, single orbit, NTD, complex congenital heart defect, absent ribs, adrenal hypoplasia, absent kidney and ureter, 2 cord vessels | Alobar/cyclops | TOP | | N/A | N/A |
| 4 | Unknown | M | Arrhinencephaly, single orbit, NTD, exomphalos | Alobar/cyclops | TOP | | N/A | N/A |
| 5 | Failed culture | F | Microcephaly, midline cleft lip and palate | Alobar | Stillborn | | N/A | N/A |
| 6 | Unknown | F | Single orbit with fused globes, proboscis, anencephaly, NTD, adrenal hypoplasia | Alobar/cyclops | TOP | | 3rd | 0 |
| 7 | 46, XX | F | Hydrocephalus, midline cleft lip and palate, hypotelorism, absent nose, low set ears, neck webbing, posterior fossa cyst, 2 accessory spleens | Alobar | 1 h | | 1st | 3 |
| 8 | 46, XX | F | Cyclops, proboscis, anencephaly, unilateral absent adrenal gland and kidney | Alobar/cyclops | TOP | | N/A | N/A |
| 9 | 46, XX | F | Microcephaly, sloping forehead, mental retardation, spastic diplegia | Semilobar | | 9·5 | 2nd | 1 |
| 10 | 46, XX | F | Non-dysmorphic, colpocephaly, mental retardation, seizures | Semilobar | | 8·0 | 1st | 1 |
| 11* | 46, XY | M | Median cleft lip and palate, arrhinencephaly, abnormal cerebellar vermis, diabetes insipidus, adrenal hypoplasia | Semilobar | 3 d | | 1st | 3 |
| 12 | Unknown | F | Median cleft lip, absent nasal septum, arrhinencephaly | Alobar | 6 d | | 1st | 1 |
| 13 | Failed culture | M | Median cleft lip and palate, absence of crista galli and ethmoid plates | Alobar | Spont abortion | | 2nd | 2 |
| 14† | 46, XY | M | Microcephaly, cebocephaly, hypotelorism, single nostril, choanal atresia, microstomia, 2 cord vessels, single hypogastric artery | Alobar | Stillborn | | 3rd | 4 |
| 15 | 46, XX | F | Central cleft lip and palate, single nostril, seizures, diabetes insipidus, abnormal temperature control | Alobar | 3·6 y | | 2nd | 0 |
| 16 | 46, XX | F | Microcephaly, iris coloboma, mental retardation, spastic quadriplegia | Semilobar | | 4·5 | 3rd | 0 |
| 17 | 46, XX | F | Microcephaly, cerebellar hypoplasia, sloping forehead, low set ears, bilateral cleft lip and palate, complex congenital heart disease | Alobar | 3 h | | 1st | 1 |
| 18 | Failed culture | F | Hydrocephalus, arrhinencephaly, cebocephaly, single orbit, central proboscis, supernumerary digit on 1 hand (so did older sib) | Alobar/cyclops | 1 h | | 2nd | 1 |
| 19 | 46, XY | M | Microcephaly, plagiocephaly, mental retardation, spastic quadriplegia | Semilobar | | 5·8 | 3rd | 0 |
| 20 | 46, XY | M | Microcephaly, hypotelorism, central cleft lip and palate, flat nose, VSD, seizures | Alobar | 5 m | | 2nd twin | 0 |
| 21 | 46, XX | F | Hypotelorism, partly occluded nostril, unilateral cleft lip, microcephaly, cerebellar hypoplasia | Semilobar | 9 m | | 1st | 1 |
| 22 | Failed culture | | Hydrocephalus, posterior fossa cyst, microphthalmia, absent optic bulbs, absent nose, bilateral cleft lip and palate, malformed low set ears, complex congenital heart defect, abnormal liver lobation | Alobar | Stillborn | | 2nd | 1 |
| 23 | 46, XX | F | Microcephaly, frontal encephalocele | Alobar | | 3·0 | 3rd | 0 |
| 24 | 46, XY | M | Frontal encephalocele, hypertelorism, exophthalmos, iris, choroid, and optic nerve colobomata, bilateral cleft lip and palate, hypoplastic cerebellum, seizures, talipes | Alobar | | 3·5 | 2nd | 0 |
| 25 | 46, XY | M | Microcephaly, iris coloboma, single nostril, bilateral cleft lip, seizures | Semilobar | 1·3 y | | 1st | 1 |
| 26‡ | 46, XX | F | Hydrocephalus, 11 pairs of ribs, 2 cord vessels | Alobar | TOP | | 3rd | 1 |
| 27 | 46, XX | F | Posterior encephalocele, cleft palate | Semilobar | 5 d | | 1st | 1 |
| 28 | 46, XX | F | Microcephaly, sloping forehead, optic nerve hypoplasia, lissencephaly, seizures | Semilobar | | 1·8 | 2nd | 0 |
| 29 | 46, XY | M | Hydrocephalus, flat forehead, hypotelorism | Alobar | | 1·5 | 1st | 1 |
| 30 | 46, XY | M | Hydrocephalus, arrhinencephaly, midline cleft lip and palate, extremely low set, malformed ears, micrognathia, 2 cord vessels | Lobar | TOP | | 2nd | 0 |
| 31‡ | 46, XX | F | Microcephaly, hypotelorism, seizures, diabetes insipidus, hypoplastic nails | Semilobar | | 1·8 | 4th | 0 |
| 32 | 46, XY | M | Extreme hypotelorism, central proboscis, accessory auricles, facial skin tag | Alobar | TOP | | 1st | 0 |
| 33 | 46, XX | F | Microcephaly, arrhinencephaly | Alobar | TOP | | 2nd | 0 |

* Sib had cerebral malformation. † Sib has single central incisor and mental retardation. ‡ Sib pair.

table also shows the severity of the lesion, the position of the affected child in the family, and the number of sibs born after the proband. Note that cases 2, 3, 7, 14, 17, 20, and 24, had abnormalities which would have been in keeping with a diagnosis of trisomy 13 but had normal karyotypes; for this reason we did not exclude patients with multiple abnormalities from the non-chromosomal group if karyotype data were not available.

### SURVIVAL AND PROGNOSIS

Nine of the 21 liveborn babies are still alive (table 4). The oldest survivor is currently aged 9·5 years. Three surviving children have alobar holoprosencephaly and all the survivors are profoundly mentally retarded. Twelve children died and approximately 60% of these deaths occurred within the first week of life (table 4).

### SEX RATIO

The overall sex ratio for non-chromosomal holoprosencephaly was 18 females:15 males and within the alobar subtype of holoprosencephaly the ratio was 11 females:10 males. For cyclopia, the ratio was three females: two males.

### PARENTS

The mean maternal age of 26·7 years (range 19–39 years) and mean paternal age of 27·4 years (range 20–36 years) were not significantly different from expected. Two sets of parents were Pakistani and first cousins, but no other parents were known to be consanguineous. One mother was a poorly controlled, insulin dependent diabetic and another took an oral contraceptive pill during the first 12 weeks of pregnancy. No other possible teratogens were identified.

### PREGNANCY OUTCOME AND PRENATAL DIAGNOSIS

Twenty-one babies (64%) with non-chromosomal holoprosencephaly were liveborn at an average gestation of 37 weeks, one pregnancy was diagnosed as a missed abortion at 16 weeks' gestation, and a further three babies were stillborn at an average gestation of 32 weeks.

A total of eight pregnancies were prenatally diagnosed by ultrasound examination and none represented a sib recurrence. All eight pregnancies were terminated. Four of these cases had an associated neural tube defect and it was the latter malformation rather than holoprosencephaly which was detected by ultrasound scanning. Two cases were terminated because of the antenatal detection of hydrocephalus and in these cases holoprosencephaly was only diagnosed at necropsy. In the remaining two cases, holoprosencephaly was diagnosed prenatally at the Regional Fetal Medicine Centre, one case having been referred from another obstetric unit at 25 weeks' gestation on account of ultrasonographically diagnosed growth retardation, the second case being diagnosed at 32 weeks' gestation when the mother presented with abdominal pain. One liveborn male infant, who had an unaffected female co-twin, was also diagnosed at 28 weeks' gestation and this pregnancy continued to term. A further liveborn child was noted to have a posterior fossa malformation

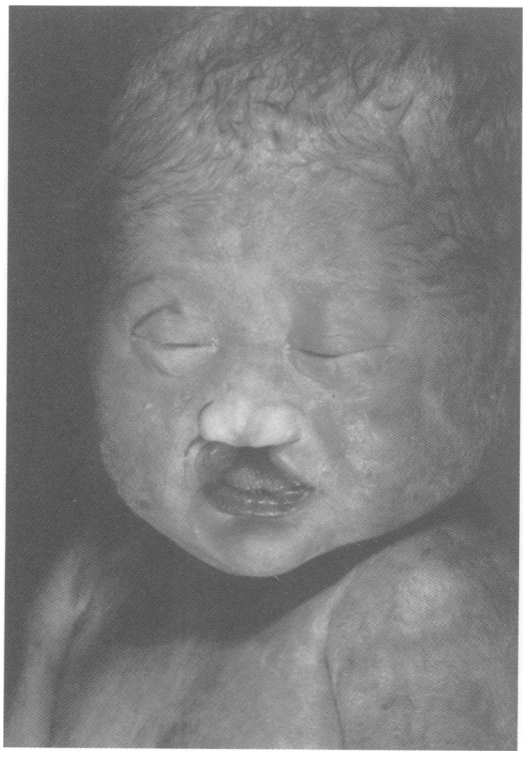

*Figure 1 Case 11. (All photographs of children reproduced with parental consent.)*

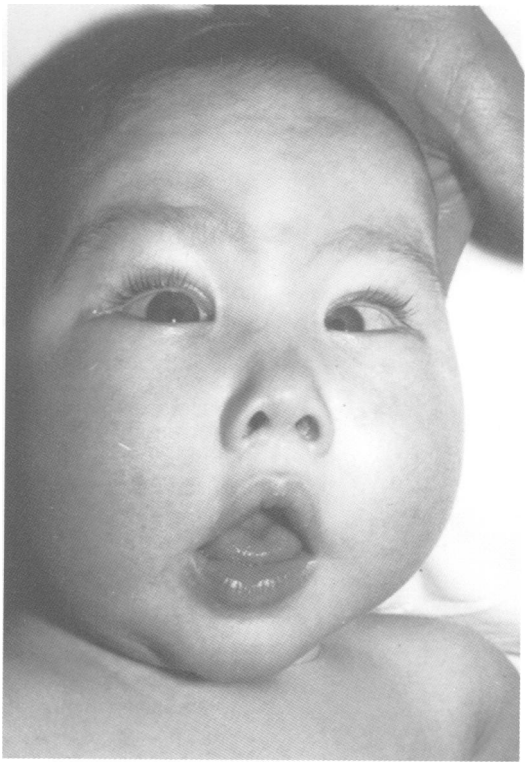

*Figure 2 Sib of case 11.*

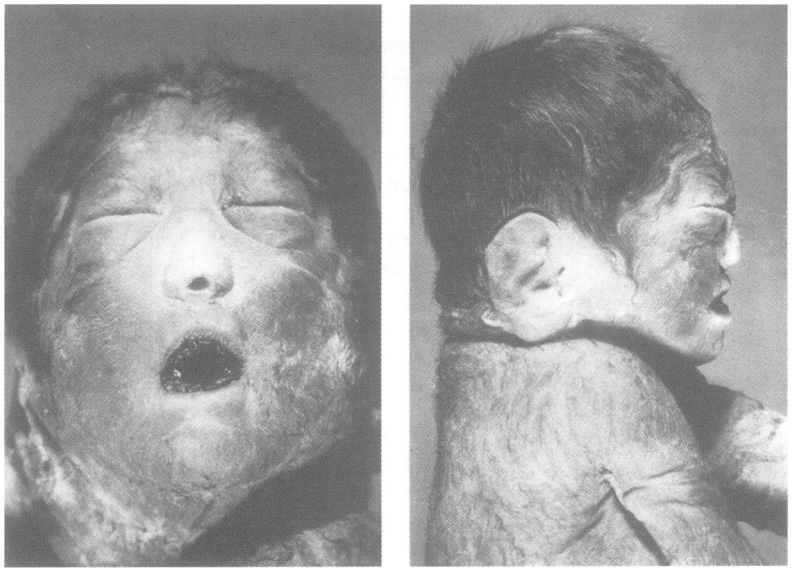

*Figure 3 Case 14.*

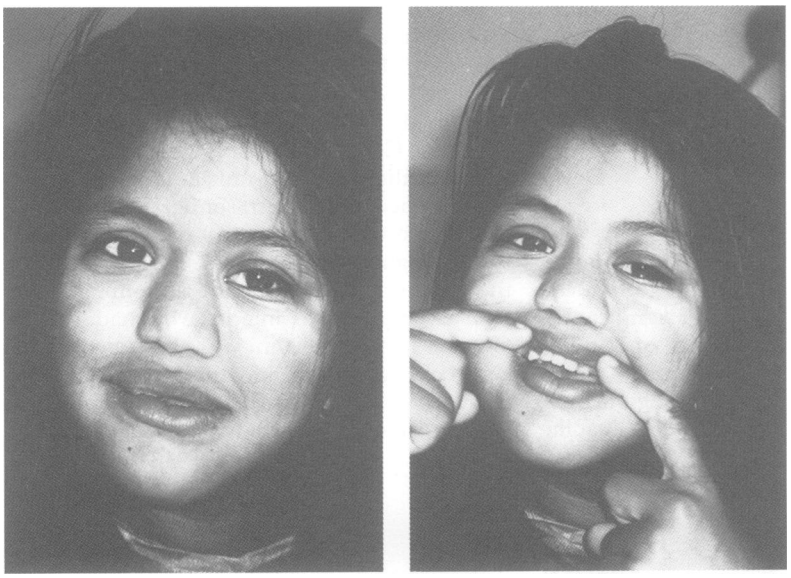

*Figure 4 Sib of case 14 showing single central incisor on right.*

at 30 weeks' gestation and postnatal cranial ultrasound examination showed semilobar holoprosencephaly in addition. Thus, accurate ultrasound prenatal diagnosis of the cerebral malformation was accomplished in only three of 33 cases (9%) with holoprosencephaly.

AFFECTED SIB PAIRS AND RECURRENCE RISK

Information regarding sibs was available for 28 families. In one family two sibs had holoprosencephaly and in two families one sib had holoprosencephaly while a second sib had another cerebral malformation. These three families are discussed in more detail.

The parents of case 11 (fig 1) are both Scottish and non-consanguineous. The first born affected child died at the age of 3 days and necropsy showed an abnormality of the cerebellar vermis in addition to holoprosencephaly. His parents subsequently had a healthy daughter but their third child, also a male, was noted from birth to have episodic tachypnoea without other clinical features of Joubert syndrome. Neuroimaging studies indicated that he had cerebellar hypoplasia and a neuronal migration disorder. On clinical examination there was an impression of mild hypotelorism (not confirmed by measurement) and midface hypoplasia (fig 2). He died at the age of 10 months and necropsy confirmed disturbed neuronal migration and cerebellar hypoplasia with underdevelopment of the cerebellar vermis. There was no abnormality of the forebrain. The proband with holoprosencephaly also had a structurally abnormal cerebellum and these male sibs were presumed to have genetically related cerebral malformations.

Case 14 (fig 3), identified through pathology department records, was the stillborn son of a Pakistani couple who were also first cousins. When the mother's obstetric case notes were examined, we realised that his older sister had previously been referred to the genetic clinic because of her dysmorphic appearance and mild-moderate mental retardation. No diagnosis was made and cranial CT scan was normal. Clinical review of the older sister revealed hypotelorism, midface hypoplasia, a broad nose, and a single central incisor with an intact sense of smell (fig 4). Both parents have normal teeth, head circumferences, and normal facial appearances. Although we cannot be certain, the facial appearance of the handicapped sib suggests she has microscopic cerebral dysgenesis that is genetically related to holoprosencephaly which affected her stillborn brother.

Case 31 (fig 5) is the child of Scottish, non-consanguineous parents. At the age of 3 months she was referred to our clinic with microcephaly and holoprosencephaly. Her mother told us that her previous pregnancy had been terminated at 25 weeks' gestation after diagnosis of hydrocephalus by ultrasound scanning. We obtained a copy of the necropsy report for this fetus (case 26, fig 6) which stated clearly that the pathological diagnosis was alobar holoprosencephaly in addition to hydrocephalus.

In summary, 23 children were born after the affected fetus or child and recurrence of holoprosencephaly was identified in one family. In two families another cerebral malformation was present in one sib. This gives an overall recurrence risk of 12% (standard error 7%) for holoprosencephaly or mental handicap or both.

## Discussion

FREQUENCY OF HOLOPROSENCEPHALY

Previous studies which noted the frequency of holoprosencephaly did not identify proportions of chromosomal and non-chromosomal cases,[13] or considered only non-chromosomal holoprosencephaly.[2] In this study, we discovered that 34% of all cases of holoprosencephaly had a cytogenetic abnormality. Thirteen patients, or three quarters of all cytogenetically abnormal patients, had trisomy 13. We identified a further seven cases of trisomy 13 from necropsy records and since these cases did not have holoprosencephaly, during our study some 65% of

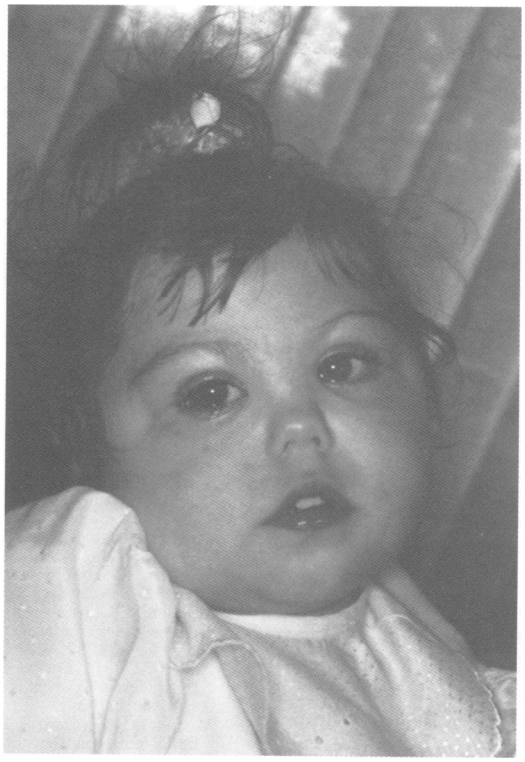

*Figure 5 Case 31.*

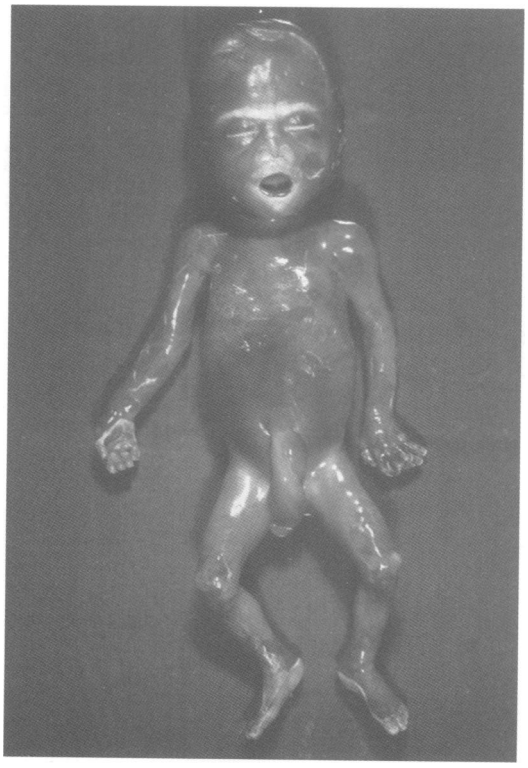

*Figure 6 Case 26 (sib of case 31).*

patients with trisomy 13 had holoprosencephaly. However, not all cases of trisomy 13 will have been ascertained from necropsy records. Therefore, we also examined the regional cytogenetic register and discovered a total of 78 cases of trisomy 13 during the study period, giving a frequency of trisomy 13 of 1:9000. Assuming that 65% of all cases of trisomy 13 have holoprosencephaly, a figure in agreement with 70% quoted by Taylor,[14] the total frequency of holoprosencephaly in fetuses and infants who were born within the west of Scotland is 1:8000, and the frequency of non-chromosomal holoprosencephaly is 1:21 000. Considering cases born after 28 weeks' gestation and using total births as the denominator, the birth prevalence estimate is 1 in 26 730. Certainly, this is a minimum estimate because of incomplete ascertainment of cases, for example, cases of semilobar and lobar holoprosencephaly may have been missed because facial signs were lacking and neuroimaging investigations were not routinely performed on children with mental retardation. Nevertheless, we regard our local population frequency and prevalence estimates as being good approximations to the true figures.

## CLINICAL FEATURES AND SEVERITY OF LESION

The clinical features of the children and fetuses with holoprosencephaly were extremely variable with all manifestations of the cerebral lesion being represented. We found that 21 patients had alobar holoprosencephaly, 11 had semilobar holoprosencephaly, and one had lobar holoprosencephaly (table 3). Five of the patients with alobar holoprosencephaly had a cyclops phenotype. The majority of patients had multiple abnormalities, with cleft lip/palate and neural tube defects being present most frequently. One important practical point which emerged is that even severely affected children with premaxillary agenesis may have prolonged survival for several years and this was not always appreciated at the time of their birth. Only three children had normal facial features (cases 2, 9, and 17). These three children are still alive and in each case holoprosencephaly was diagnosed by neuroimaging when investigating mental retardation and seizures. Therefore, as in previous studies, we found the "face predicts the brain" in most but not all children with holoprosencephaly and the majority of patients with the facial features of holoprosencephaly have alobar holoprosencephaly.

## GENETIC COUNSELLING AND PRENATAL DIAGNOSIS

We found that 28 cases had a total of 23 subsequent sibs and three sib pairs were identified. In two families the proband was the second affected child because the first child/fetus was not diagnosed as affected by holoprosencephaly. Only one sib had holoprosencephaly but, on clinical grounds, there was evidence that the affected sibs had a related cerebral malformation. Thus, in this small study the "recurrence risk" for non-chromosomal holoprosencephaly and related cerebral malformations is 12% (standard error 7%). Although this is greater than the 6% recurrence risk figure calculated by Roach *et al*,[2] in our study, the recurrence risk will decrease if more unaffected sibs are born, and as only 10 mothers had their last pregnancy more than

five years ago, there is a possibility that some families are not yet complete.

In 1985 Chervenak *et al*[15] reported ultrasound prenatal diagnosis of alobar holoprosencephaly and in our series, which extended from 1975 to 1994, only three cases with alobar holoprosencephaly were diagnosed by prenatal scans at Regional Fetal Medicine Centres. Unfortunately we could not establish the number of times an affected fetus was subject to detailed ultrasound examination and holoprosencephaly was missed. Certainly, in the three families where there was recurrence of holoprosencephaly or a related cerebral malformation, each fetus underwent detailed ultrasound examination at the local hospital. However, there were reasons for missing the recurrence in each case: in the first the affected sib had cerebellar vermis aplasia, which is probably more difficult to detect; in the second family, although the ultrasonographer was aware that there was a sib with mental handicap and malar hypoplasia, it was not recognised that this could be related to holoprosencephaly; in the third family, recurrence of holoprosencephaly was missed, but perhaps the contributory factor was mistaken diagnosis of hydrocephalus in the proband. Finally, in respect of prenatal diagnosis, it is notable that six cases (20%) with non-chromosomal holoprosencephaly had a posterior fossa abnormality, and also that cerebellar vermis aplasia was the major intracranial sign of recurrence in one family. We therefore suggest that when detailed ultrasonographic evaluation of the fetus is indicated on account of a previous family history of holoprosencephaly, special attention is paid to the fetal posterior fossa and the significance of any abnormality therein is carefully considered, even in the presence of normal hemispheric division. We would also suggest that the ultrasonographic evaluation is carried out at the most experienced centre available.

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